Journal of the International Neuropsychological Society (2001), **7**, 27–32.

Long-term effects of high-dose zidovudine treatment on neuropsychological performance in mildly symptomatic HIV-positive patients: Results of a randomized, double-blind, placebo-controlled investigation

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(RECEIVED July 17, 1997; REVISED December 20, 1999; ACCEPTED January 3, 2000)

Abstract

This study examined the treatment outcome of high-dose (1500 mg/day) zidovudine (AZT) on neuropsychological (NP) functioning (Trailmaking Test A & B, WAIS-R Digit Symbol, and Rey Auditory Verbal Learning Test) across a 12-month period in mildly symptomatic HIV-1 seropositive men ($n = 46$ at entry) enrolled in a randomized, double-blind, placebo-controlled trial (VA Cooperative Studies Program #298). Neither short-term (0–6 months) nor long-term (0–12 months) AZT administration revealed enhancement in NP performance. The results suggest that, although AZT may afford patients prophylactic benefits, protracted high-dose AZT treatment does not improve NP functioning in mildly symptomatic HIV-positive individuals. (*JINS*, 2001, *7*, 27–32)

Keywords: HIV-1, Prolonged AZT administration, Neuropsychological outcome

INTRODUCTION

Significant improvements in neuropsychological (NP) functioning following the administration of high-dose zidovudine (AZT) treatment have been reported in individuals with AIDS (Schmitt et al., 1988) and AIDS dementia complex (Riccio et al., 1990; Sidtis et al., 1993; Tozzi et al., 1993; Yarchoan et al., 1988). Sidtis et al. (1993) reported improvements on measures of verbal fluency, attention-concentration, and motor functioning subsequent to administration of 2000 mg/day of AZT. However, they only examined NP gains through 16 weeks of treatment without further assessment using a double-blind, placebo-controlled protocol. Therefore, the protracted effects of AZT treatment on NP functioning beyond 16 weeks remain unknown.

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Schmitt et al. (1988) reported similar improvements in individuals diagnosed with AIDS and AIDS-related complex after 16 weeks of AZT treatment (1500 mg/day). Improvements were observed in a select number of NP domains, including sustained attention, verbal memory (consistent long-term retrieval), and visual-motor functioning. However, this study also was terminated without further long-term assessment of the efficacy of AZT, and the majority of treatment benefits only were evidenced in patients with AIDS-defining conditions.

Other studies have found benefits during the course of 6 months as a result of AZT treatment in patients with AIDS (Karlsen et al., 1995; Reinvang et al., 1991). Unfortunately, several of these studies have been quasi-experimental in nature (i.e., no control group, unrandomized) or have used open-label paradigms or have failed to assess NP improvements by placebo-controlled methodologies (see Tozzi et al., 1993). These experimental shortcomings have complicated their interpretation and limited their generalization.

Investigators also have reported declines in the occurrence of neuropathology and AIDS-related dementia subsequent to the introduction of AZT (Portegies et al., 1989). However, it is possible that this association is the result of other intervening factors unrelated to the introduction of AZT treatment, such as refinements in the diagnostic criteria for HIV-related dementia or the advent of more complex and sophisticated antiretroviral treatment combinations (e.g., AZT and ddC). Furthermore, although the incidence of AIDS-related dementia did not increase between 1985 and 1992, coinciding with the widespread administration of AZT, its extensive use did not lower the incidence of dementia associated with AIDS (Bacellar et al., 1994).

Although advantageous effects on neuropsychological functioning subsequent to brief AZT treatment, and transient improvements as a result of long-term AZT administration, have been reported in the literature for patients with AIDS and AIDS dementia complex, there is limited data addressing the effects of prolonged (long-term) high-dose AZT treatment on neurocognitive functioning of mildly symptomatic HIV-positive individuals. This limitation in the literature is unfortunate because HIV-positive individuals who are only mildly symptomatic have been known to experience signs of early central nervous system involvement (Grant et al., 1987) and mild-subtle neuropsychological impediments (Bornstein et al., 1992).

The present study longitudinally examined the efficacy of high-dose (Fischl et al., 1990) AZT treatment (1500 mg/day) on NP functioning in a sample of individuals with mild HIV-associated symptoms. In contrast to the studies previously cited, which either assessed the short-term NP outcome of AZT or employed quasi-experimental approaches to evaluate its long-term efficacy, the present investigation evaluated the effects of AZT during the course of 12 months (1988–1989) in patients enrolled in a randomized, double-blind, placebo-controlled trial (Hamilton et al., 1992). Although the clinical trial was later changed to an open-label protocol for ethical reasons, following the guidelines of the Centers for Disease Control (CDC) supporting the prophylactic value of AZT (CDC, 1989), the data presented in this investigation only includes participants enrolled prior to this modification in treatment protocol.

This investigation is limited to the effects of AZT monotherapy, considered the treatment of choice at the time the parent investigation (Hamilton et al., 1992) was conducted, and prior to the development of more complex antiretroviral treatment combinations (cf., Cotton & Friedland, 1992) or protease inhibitors (Robins & Plattner, 1993). However, viewed within the current complex combination therapy context, the present study attempts to provide critical information regarding the individual effects of AZT, as AZT monotherapy continues to be used to treat patients who are unable to tolerate combination therapies of greater complexity (e.g., HAART) or for whom combination therapy has been ineffective (cf., Bassetti et al., 1999). Finally, although AZT monotherapy has been replaced by more refined or potent treatment combinations, and is seldom the treatment of choice in the U.S.A., AZT remains the primary antiretroviral pharmacotherapy in other countries worldwide, particularly in regions with high, or rapidly increasing, HIV incidence and prevalence.

METHOD

Subjects

Neuropsychological data from 46 patients at study entry were available for analysis. The lower number of patients used for analyses at 6 and 12 months was due to missing data (attrition as a result of deaths, exclusion criteria, drop-outs, etc.). All participants were enrolled in the West Los Angeles site of the Veterans Affairs Cooperative Studies Program #298 (Hamilton et al., 1992).

Cooperative Study #298 was a randomized, double-blind, placebo-controlled investigation of the effects of early *versus* late AZT treatment in persons suffering from symptomatic HIV infection but with no AIDS-defining illnesses. Entry requirements for Study #298 were two or more physical symptoms (e.g., thrush, oral hairy leukoplakia, etc.) thought to be HIV-related and two consecutive CD4+ lymphocyte concentration counts between 200 and 500/mm^3. As previously noted, subsequent to the 1989 CDC publication guidelines advising of the prophylactic effects of AZT, patients who did not wish to continue receiving blind therapy were offered open-label AZT for ethical reasons. Prior to this modification in protocol design, the study remained a double-blind investigation [see Hamilton et al. (1992) for a complete description of recruitment and enrollment criteria, study factors associated with side effects, as well as participant treatment compliance].

Materials

Participants were administered the Trailmaking Test A & B (Trails A & B; Reitan & Wolfson, 1985), the WAIS-R Digit Symbol subtest (DSy) (Wechsler, 1981), and the Rey Auditory Verbal Learning Test (RAVLT) (Rey, 1964). These instruments were selected on the basis of previous research documenting their sensitivity in detecting early HIV-related neurocognitive changes (Tross et al., 1988; van Gorp et al., 1989) and the effects of medication capable of affecting central nervous system (CNS) functions (Trimble & Thompson, 1986). The Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960) was used to determine differences in depressive symptomatology between the two study groups (AZT *vs.* Placebo) at entry.

Procedure

Patients were randomly assigned to receive either active AZT or placebo. Half ($n = 23$) received active medication (1500 mg/day) and half ($n = 23$) received a placebo in a double-blind fashion at entry. All subjects were administered the Trailmaking Test A & B, the WAIS-R Digit Symbol subtest,

https://doi.org/10.1017/S1355617701711034 Published online by Cambridge University Press

Table 1. Demographic, immunologic, and emotional variables by subject group at study entry

	Group		
	AZT	Placebo	
Variable	M(SD)	M(SD)	Statistical test
Age (years)	43.8(10.5)	43.9(10.1)	$t = .03$, $DF = 44$, $p > .10$
Education (years)	13.7 (1.4)	14.1 (2.6)	$t = .64$, $DF = 44$, $p > .10$
Occupational status	1.4 (.73)	1.5 (.68)	$t = .44$, $DF = 44$, $p > .10$
CD4+ count (/mm^3)	359.6 (156)	306.8 (124)	$t = 1.2$, $DF = 44$, $p > .10$
HRSD	15.4 (10)	11.9 (8.1)	$t = 1.9$, $DF = 44$, $p > .09$

and the RAVLT at the onset of the study and subsequently at 6- and 12-month intervals. Subjects with prior drug or alcohol abuse or dependence, or prior neurologic illness or learning disability were excluded from this study. Blood tests were conducted throughout the study to monitor participants' compliance with the assigned AZT or placebo arm of the study (see Hamilton et al., 1992).

RESULTS

Table 1 shows group (AZT; placebo) means and standard deviations for demographic, immunologic, and other (e.g., depressive symptomatology) variables. These data were analyzed using Fisher's Exact *t* tests.

Comparisons between the participants receiving AZT *versus* placebo at entry revealed no statistically significant differences in demographics. Immunological status as measured by CD4+ count (/mm^3) at entry also failed to reveal statistically significant group differences. Demographic and immunologic analyses conducted from data available at 6- and 12-month follow-ups yielded comparable results. In addition, no statistically significant differences were evidenced at entry in depressive symptomatology as measured by the HRSD between the participants receiving AZT relative to the group receiving placebo.

Evaluation of Efficacy at 6 Months

To assess treatment effects at 6 months, longitudinal neuropsychological data ($n = 33$) for the 0- to 6-month comparison (Waves 0 and 1) were submitted to a Group (AZT; placebo) $\times$ Trial (0 and 6 months) repeated measures Analysis of Variance (ANOVA). Table 2 shows group means and standard deviations for all tests across trials. This analysis revealed no significant Group effect. In fact, the results only revealed a significant effect for Trial (time) on Trails A for both groups ($F[1,31] = 4.23$, $p < .048$). The significant Trial effect was most likely the result of test–retest learning subsequent to multiple test exposure. No other results revealed statistically significant differences.

Evaluation of Efficacy at 12 Months

In an attempt to assess the prolonged efficacy of AZT on neuropsychological functioning, longitudinal NP data ($n = 26$) from subjects who had remained in the two original arms (AZT; placebo) of the study for 12 months since entry (Waves 0, 1, and 2) also were submitted to a Group (AZT; placebo) $\times$ Trials (0, 6, 12 months) repeated measures ANOVA as before. Table 3 shows group means and standard deviations for all tests across trials. This analysis failed to show statistically significant Group or Trial differences for any of the neuropsychological measures. Although splitting the AZT group into two subgroups (e.g., high *vs.* low responders) for further analysis would have been ideal, as it would have allowed for a comparison within the subset of participants who received AZT, only 11 subjects were available in the AZT group at this time point precluding a meaningful analysis (see Kirk, 1982).

Evaluation of Individual Treatment Gains

Although the present investigation did not reveal significant *group* (mean) effects as a result of prolonged AZT treatment, further quantitative analyses were conducted at 12 months to determine if individual participants administered AZT in the study benefited from treatment gains that might have been otherwise masked by the analyses of group data. For this analysis, each individual's neuropsychological score for each of the four procedures administered at 12 months

Table 2. Longitudinal (0–6 months) neuropsychological data—group means and (standard deviations)

Group	Procedure	Baseline	6 months
		($n = 33$)	($n = 33$)
AZT	Trails A[a]	38.6(13.3)	32.1(16.4)
	Trails B[a]	86.3(14.4)	86.4 (8.3)
	WAIS-R (DSy)[b]	47.9 (3.1)	52.4 (4.2)
	RAVLT[c]	45.4 (4.8)	45.4 (5.2)
Placebo	Trails A	33.2 (5.6)	31.5 (5.3)
	Trails B	82.3 (6.7)	75.2 (7.3)
	WAIS-R (DSy)	51.7 (2.2)	52.3 (2.8)
	RAVLT	44.7 (3.1)	46.7 (5.5)

[a]Trails A & B scores represent completion time (seconds).
[b]Digit symbol scores represent total number of symbols copied.
[c]RAVLT scores represent number of words (Trails 1–5).

https://doi.org/10.1017/S1355617701711034 Published online by Cambridge University Press

Table 3. Longitudinal (0–12 months) neuropsychological data—group means and (standard deviations)

Group	Procedure	Baseline	6 months	12 months
		(n = 26)	(n = 26)	(n = 26)
AZT	Trails A[a]	34.8(10.2)	31 (12.2)	31.1(10.4)
	Trails B[a]	73.3(12.2)	80.7(14.7)	73 (9.4)
	WAIS-R (DSy)[b]	49.7 (4.8)	54.3 (4.7)	53.1 (5.2)
	RAVLT[c]	46.3 (4.3)	45.2 (4.6)	49.9 (4.6)
Placebo	Trails A	33.1 (8.4)	30 (7.8)	31.1 (7.2)
	Trails B	78.4 (7.2)	70.2 (7.5)	70.3 (7.0)
	WAIS-R (DSy)	51.6 (2.3)	52.6 (2.8)	52.4 (3.2)
	RAVLT	46.8 (2.2)	49.4 (3.2)	48.6 (2.1)

[a]Trails A & B scores represent completion time (seconds).
[b]Digit symbol scores represent total number of symbols copied.
[c]RAVLT scores represent number of words (Trails 1–5).

were subtracted from their group mean for each procedure to determine if the magnitude of their difference reached or surpassed two standard deviations. However, this analysis did not reveal significant improvements in any of the neuropsychological measures either. Although two standard deviations may seem rather conservative, it should be noted that four scores (one for each procedure) for each participant were evaluated increasing the probability of a significant but spurious score simply as a result of chance.

DISCUSSION

The results did not reveal group improvements subsequent to AZT administration over the 6- or 12-month periods on any of the neuropsychological measures. Because the analysis of group data did not reveal long-term NP benefits as a result of long-term AZT exposure, and because the group analysis might have concealed individual gains, the treatment outcome for each subject was examined. Unfortunately, these results also failed to show evidence of individual neurocognitive improvements in this group of mildly symptomatic patients.

The present results are consistent with recent research that assessed the NP effects of HIV at different disease stages. Heaton et al. (1995) found identical impairment rates for AZT treated or untreated participants in the HIV-positive CDC B and C categories in their investigation. The current results also are congruent with data suggesting transient benefits of AZT in a group of patients with AIDS (Karlsen et al., 1995) who, despite observable NP improvements at 6 months, exhibited declines in NP performance during a 12-month follow-up (cf., Shepp et al., 1997 for a discussion on AZT tolerance). Similarly, the current findings support data from research assessing the effects of other pharmacological treatments on neuropsychological functioning. For example, Mapou et al. (1996) have demonstrated that interferon alfa-n3 was incapable of producing significant and sustained neurocognitive benefits in asymptomatic or mildly symptomatic HIV-positive individuals.

Our results are at odds with a select number of findings from several studies assessing the short-term effects of AZT on NP functioning. However, several methodological factors could account for the differences in findings (cf., Bornstein, 1994). Unlike Schmitt et al. (1988) and Sidtis et al. (1993), whose trials used individuals with AIDS dementia complex and/or AIDS, we assessed the impact of AZT in mildly symptomatic individuals with non-AIDS-defining illnesses. Therefore, our failure to observe neurocognitive "gains" in this relatively intact sample, relative to other investigations, may be associated with their stage of HIV-infection and clinical symptomatology, as well as degree of NP impairment at the time of entry in the study. In fact, it should be noted that although Schmitt et al. (1988) reported NP increments in performance in all patient groups, the majority of improvements were evidenced in patients with AIDS-defining conditions (group with greater degree of disease involvement), consistent with the present findings given the mildly symptomatic status of the participants. Another limitation that could possibly account for the differences in findings due to short-term AZT administration (0–6 months) is the lack of statistical power afforded by this study in comparison with past research, which used a larger number of participants (e.g., Schmitt et al., 1988). Although our investigation did not reveal benefits from short- or long-term AZT treatment, individually or as a group, our small number of subjects may not have afforded the necessary statistical power to demonstrate a significant effect on the various neuropsychological domains assessed. This study additionally evaluated the effects of AZT on NP functioning through the recruitment of subjects from the Veterans Affairs Cooperative Studies Program #298 (Hamilton et al., 1992) on the basis of their CD4+ count as one of the primary selection criteria. Unfortunately, research investigating the effects of HIV on neuropsychological performance has indicated that this marker is weakly associated with NP functioning (see Podraza et al., 1994 for asymptomatic patients). Differences in findings also may be associated with the sensitivity of the NP procedures employed in this inves-

https://doi.org/10.1017/S1355617701711034 Published online by Cambridge University Press

tigation relative to that of previous studies. For example, in Schmitt et al.'s (1988) study, differences were not evidenced between the participants receiving AZT relative to those receiving placebo on a digit span test or on a measure of verbal memory (long-term storage), the latter similar to the verbal memory instrument used in this investigation (RAVLT). However, significant group differences benefiting the AZT group were evidenced when more sensitive sustained attention (Two and Seven Test) or verbal memory (consistent long-term retrieval) procedures were employed. Other investigators (cf., Miller & Wilkie, 1994) also have argued for the use of measures with greater sensitivity (e.g., reaction time task) capable of detecting subtle neurocognitive HIV-related changes. Unfortunately, such procedures were not utilized in this investigation. Finally, drug dose may have accounted for the differences in findings. Although both treatment protocols could be considered "high doses" (Fischl et al., 1990), Sidtis et al. (1993) administered 2000 mg/day compared to the 1500 mg/day administered in this investigation.

The present results do not suggest that AZT is incapable of improving neuropsychological functioning in HIV-positive individuals. As indicated by other researchers (Arendt et al., 1991; Sidtis et al., 1993), it appears that AZT produces significant improvements on neurological substrates and NP performance during the advanced stages of the disease (Yarchoan et al., 1988). In addition, other researchers (Graham et al., 1992) have demonstrated that AZT treatment usually affords countless medical benefits to the patient, including prophylaxis against opportunistic diseases. Therefore, the present findings are limited to the NP benefits of *prolonged* exposure to AZT in HIV-positive *mildly* symptomatic individuals.

In summary, this study examined the protracted (12-month) effects of AZT monotherapy (1500 mg/day) treatment on neurocognition in a group of HIV-positive mildly symptomatic participants. The present results failed to exhibit NP improvements associated with this treatment regimen. Despite the lack of NP gains associated with prolonged AZT exposure during the mildly symptomatic stages, the use of AZT is warranted immediately after detection of human immunodeficiency virus infection for vital medical reasons, including diminished susceptibility to opportunistic diseases. In addition, although AZT monotherapy is no longer considered the standard of care, and increasingly complex antiretroviral treatment combinations in conjunction with protease inhibitors have replaced AZT alone as the treatment of choice, not all patients respond positively or tolerate complex therapy combinations and AZT monotherapy remains a viable and life-sustaining alternative for these patients.

ACKNOWLEDGMENTS

This research was partially supported by a Fogarty AIDS International Foundation-UCLA CIRID grant No. TW00003-07 to Antolin M. Llorente and a National Institute of Health Grant No. 4-484700-312788 to Paul Satz and Wilfred G. van Gorp. The authors sincerely thank all the volunteers who participated in the study. The authors also express their gratitude to Jackie Foster and Steven G. Holston for their assistance coordinating information related to this research and to three anonymous reviewers for their useful comments and reviews. Portions of these data were presented at the Pathogenesis of HIV Infection of the Brain: Impact on Function and Behavior, Chantilly, Virginia (1994, April) sponsored by the Office on AIDS and the Division of Neuroscience and Behavioral Science, National Institute of Mental Health.

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